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EXAMINER	
MYERS, CARLA J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,286	AIACH ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☒ Claim(s) *1-9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, and methods for detecting the presence of each of the polymorphisms at positions 139, 744, and 801 of intron 1 and position 52 of exon 2 in the reply filed on August 14, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-9 have been examined herein.

Claims 10-13 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Objections

3. Claims 1-9 are objected to because of the following informalities:

Claims 1-3 are objected to because in claim 1 "[position" should read "position."

Claims 4-5 are objected to because in claim 4, line 6, "H@" should read "H2."

Claims 4-5 are objected to because in claim 4, line 8, "anhy" should read "any."

Claims 6-9 are objected to because in claim 6, line 8, the following phrase is duplicative and should be deleted: "and presence 744 of the intron, insertion of A at position 801 of the intron,".

Claims 6-9 are objected to because in claim 6, line 6, "position**s** 52" should read "position 52."

Specification

4. The disclosure is objected to because of the following informalities:

On page 11, the text at lines 21 and 22 is not readable because it appears to have been lined through.

Appropriate correction is required.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-25 because the previously submitted Sequence Listing does not include each of the sequences set forth in the present application. See, for example, page 4, Table 1 of the specification. In response to this Office action, Applicants must comply with the requirements of 37 CFR 1.821-1.825. In particular, Applicant is required to submit a new CRF and paper copy of the Sequence Listing containing the additional sequence, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same. See the attached Notice to Comply.

Claim Rejections - 35 USC § 112 – second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-9 are indefinite. The claims are drawn to a method for identifying at least one polymorphism of a haplotype. However, the claims recite a step of analyzing a region located around positions 139, 744, and 801 of intron 1 and position 52 of exon 2, wherein the simultaneous presence of each of a T at position 139, a C at position 744, an insertion of an A at position 801 and the presence of a T at position 52 designate haplotype H2, wherein the presence of haplotype H2 is indicative of higher risk of developing thrombosis and lower sensitivity toward a thienopyridine therapy. Thereby, it is unclear as to whether the claims are intended to be limited to methods which detect only one polymorphism or methods which detect each of the 4 polymorphisms. In the former case, it is not clear as to how the recitation regarding each of the 4 polymorphisms relates back to the remainder of the claim – i.e., it is unclear as to the relevance of the fact that the presence of the H2 haplotype indicates a higher risk of developing thrombosis and lower sensitivity toward a thienopyridine therapy if the method is one which detects only one polymorphism. It is also unclear as to the relationship between the 4 polymorphisms and the method step recited in the claims since the claims recite analyzing the region around the polymorphisms at positions 139, 744, and 801 of intron 1 and position 52 of exon 2, but the claims do not actually recite determining the nucleotide present at positions 139, 744, and 801 of intron 1 and position 52 of exon 2. Accordingly, it is unclear as to what is intended to be the meets and bounds of the claimed subject matter.

Claim 8 is indefinite because the phrase "said region(s) of the genomic DNA" because this phrase lacks proper antecedent basis. While the claim previous refers to

"regions of $P2Y_{12}$ receptor gene" the claim does not previous refer to a region or regions of the genomic DNA.

Claim Rejections - 35 USC § 112 - Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for determining a risk of peripheral arterial disease (PAD) in a human subject comprising (a) providing a nucleic acid sample from a human subject wherein said nucleic acid sample comprises a $P2Y_{12}$ receptor nucleic acid sequence; (b) analyzing the $P2Y_{12}$ receptor nucleic acid sequence to determine the nucleotides present at nucleotide positions 139, 744 and 801 of intron 1 (SEQ ID NO: 1) and at nucleotide position 801 of exon 2 (SEQ ID NO: 2), wherein the simultaneous presence of a T at position 139 of intron 1, the presence of a C at position 744 of intron 1, an insertion of an A at position 801 of intron 1, and the presence of a T at position 52 of exon 2 is designated a H2 haplotype; and (c) determining that said human subject is at a higher risk of developing PAD when the H2 haplotype is present on at least one allele in comparison to a control subject without any H2 allele, and wherein said human subject is a Caucasian male,

does not reasonably provide enablement for methods for determining risk of developing any thrombosis in any subject, methods for determining sensitivity to any thienopyridine therapy in any subject, or methods for identifying a polymorphism of a

haplotype of a $P2Y_{12}$ associated with thrombosis or with lower sensitivity to a thienopyridine therapy by analyzing regions of the $P2Y_{12}$ receptor gene located around positions 139, 744, 801 of intron 1 and position 52 of exon 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1-3 are broadly drawn to methods for determining risk of developing any thrombosis in any subject by determining the presence of a H2 haplotype in the $P2Y_{12}$ receptor gene, wherein the H2 haplotype consists of a T at position 139 of intron 1, a C at position 744 of intron 1, an insertion of an A at position 801 of intron 1, and a T at position 52 of exon 2. Claims 4-5 are drawn to methods for determining the sensitivity of any subject to any thienopyridine therapy by assaying for the presence of the H2 haplotype, as defined above. Claims 6-9 are drawn to methods for identifying at least one polymorphism in a haplotype of the $P2Y_{12}$ receptor gene by analyzing a genomic DNA sample for regions of the $P2Y_{12}$ receptor gene around nucleotide positions 139, 744, and 801 of intron 1 (SEQ ID NO: 1) and position 52 of exon 2 (SEQ ID NO: 2),

wherein it is a property of a H2 haplotype that it is indicative of a higher risk of developing thrombosis or a lower sensitivity to thienopyridine therapy as compared to a control subject.

As broadly written, claims 1-9 encompass the analysis of any "subject." As defined on page 3 of the specification, a subject is any human patient or any mammal or vertebrate. Thereby, the claims encompass the analysis of widely diverse species such as rabbits, dogs, monkeys, elephants, pandas, fish, frogs, birds, etc.

Additionally, claims 1-9 include the analysis of human subjects of any ethnic background and both male and female human subjects.

Claims 1 and 6-9 encompass the determination of a risk of developing any type of thrombosis (claim 1) and the detection of subjects carrying a H2 allele, wherein the H2 allele is indicative of a higher risk of developing any type of thrombosis. Claim 2 is limited to methods for determining risk of any arterial thrombosis (claims 6-9). The specification (page 7) states that thrombosis "encompasses other thrombotic states such as venous thrombosis and venous thromboembolic diseases, as well as thrombotic microangiopathy or intravascular disseminated coagulation." Thereby, the claims encompass the determination of risk of a distinct disorders, that differ from one another with respect to their etiology and symptomology. The claims appear to include the determination of deep vein thrombosis (claims 1 and 6-9), pulmonary embolism, superficial thrombosis, post-thrombotic syndrome, heart attacks, strokes etc, as well as peripheral arterial disease.

Claims 4 and 6-9 encompass methods for the determination of a subject's sensitivity to any thienopyridine therapy (claim 4) and the detection of a subjects carrying a H2 allele, wherein the H2 allele is indicative of a higher sensitivity to any thienopyridine (claims 6-9). Thereby the claims encompass the determination of sensitivity to any type of thienopyridine compound or derivative thereof, wherein the compounds may differ from one another with respect to their structure and biological activity.

Additionally, the claims do not recite a particular means for identifying the polymorphisms, and thereby encompass indirectly detecting the polymorphisms by assaying for a biological activity or by assaying for polymorphisms or haplotypes that are in linkage disequilibrium with the H2 haplotype, or the individual polymorphisms at positions 139, 744 and 801 of intron 1 and position 52 of exon 2. In particular, claims 6-9 encompass identifying a polymorphism of a haplotype by analyzing genomic DNA at any positions "around" positions 139, 744 and 801 of intron 1 and position 52 of exon 2.

Nature of the Invention

The claims are drawn to methods for determining a subject's risk of thrombosis or sensitivity to a thienopyridine by assaying for a H2 haplotype. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches that the nucleotide sequence of the human, mouse, rat, and macaque $P2Y_{12}$ receptor gene were known at the time the invention was made (page 3). The specification (page 5) further teaches a H2 haplotype of the $P2Y_{12}$ receptor gene, wherein the H2 haplotype consists of a T at position 139 of intron 1, a C at position 744 of intron 1, an insertion of an A at position 801 of intron 1, and a T at position 52 of exon 2.

The specification (Example 2, beginning at page 20) teaches the results of an genotype analysis of Caucasian males having peripheral arterial disease (PAD). The specification (page 21) reports that "Among PAD patients, 30% of the subjects were carriers of at least one H2 allele compared to 21% in the control group (p=0.03)." Accordingly, the specification has established an association between the presence of at least one H2 allele and PAD in Caucasian male subjects. However, the specification does not provide any information on the frequency of the H2 allele in subjects having non-PAD types of thrombosis, including the various types of vein thrombosis. Further, the specification does not provide any information on the frequency of the H2 allele in female subjects or in non-Caucasian subjects. There is also no disclosure regarding the occurrence of the H2 allele in non-human organisms.

Regarding sensitivity to thienopyridine compounds, the specification (Example 1, beginning at page 13) teaches the results of a genotyping study of 98 Caucasian male subjects aged from 18 to 35 years. The specification (e.g., page 17) reports that subjects carrying at least one H2 allele had a higher maximal aggregation in response to ADP as compared to subjects not carrying a H2 allele. The specification (page 18)

also reports that the higher maximal aggregation "was related, at least in part, to differences in the mechanism regulating cAMP inhibition by ADP." At page 19, the specification states:

> Data obtained with specific $P2Y_{12}$ receptor inhibitors such as the thienopyridines ticlopidine and clopidogrel confirm that P2Y12 is the only known platelet ADP receptor responsible for adenylate cyclase inhibition and the subsequent reduction in intracellular camp (Geiger et al., 1999). Moreover, selective P2Y1 receptor antagonists have no effect on ADP-induced adenylate cyclase inhibition (Jin et al., 1998a). Thus, the difference in the platelet cAMP concentration between carriers and non carriers of the H2 haplotype after ADP stimulation is a plausible explanation for the difference in maximal ADP-induced aggregation observed in these two groups of subjects, although we cannot rule out the involvement of adenylate cyclase-independent mechanisms (Kauffenstein et al., 2001).

The specification also acknowledges that the molecular mechanism by which the H2 haplotype increases platelet aggregation in response to ADP remains to be determined. The specification does not provide any data clearly establishing an association between sensitivity to the a thienopyridine and the H2 haplotype, or a specific showing of the relationship of human subjects to thienopyridine therapy and higher maximal aggregation in response to ADP.

The Predictability or Unpredictability of the Art :

The art of determining an association between a polymorphism and a phenotype is highly unpredictable. Knowledge that a polymorphism is associated with one type of disease, such as PAD, does not allow one to conclude which, if any, additional diseases will also be associated with the presence of a polymorphism. The specification (page 19) acknowledges that the mechanism by which the H2 haplotype increases platelet aggregation in response to ADP has not yet been determined. In the absence of a clear

structure-function relationship, one cannot predictably extrapolate the results obtained with PAD to other types of thrombosis.

The unpredictability of extrapolating the results obtained with PAD to other types of thrombosis is supported by the teachings in the post-filing date art. In particular, Schettert (Thrombosis Research. 2006. 118: 679-683; see, e.g., page 683) reported that there was no association between the H2 haplotype and chronic cardiovascular disease.

Regarding claims 4-9, it is unpredictable as to whether the H2 allele is associated with sensitivity to a thienopyridine drug. The data provided in the specification (Example 1) is limited to platelet aggregation in response to ADP and the differences in cAMP concentrations between H2 carriers and non-carriers. While the specification (page 19) suggests that differences in cAMP concentrations between H2 carriers and non-carriers may explain the differences in maximal ADP-induced platelet aggregation, the specification has not established that there is a direct and clear relationship between maximal ADP-induced platelet aggregation and response to any thienopyridine drug. In the absence of any information regarding the frequency of the H2 haplotype in subjects that have a higher sensitivity to thienopyridines, such as ticlopidine and clopidogrel, and in the absence of a clear structure-function relationship between the H2 haplotype and response to thienopyridines, it remains highly unpredictable as to whether the H2 haplotype is correlated with response to as ticlopidine and clopidogrel, or other thienopyridine derivatives. This unpredictability is supported by the teachings in the post-filing date art. For instance, Angiolillo (Thrombosis Research. 2005. 116: 491-497)

studied the frequency of the T744C polymorphism of the H2 haplotype in patients with coronary artery disease treated with the thienopyridine clopidogrel. Angiolillo determined that the T744C polymorphism does not modulate platelet response to clopidogrel. The reference concludes that "(t)his specific gene polymorphism alone is therefore unlikely to be the cause of variability in individual response to antiplatelet therapy" (page 496, col. 2). Similarly, Lev (Thrombosis Research. 2007. 119: 355-360) also determined that there was no association between the T744C P2Y12 receptor polymorphism and response to clopidogrel (page 359, col. 2).

It is also highly unpredictable as to whether the results obtained in Caucasian subjects can be extrapolated to subjects of other ethnic groups and to female subjects. The teachings in the specification support this unpredictability in that the specification teaches that the D allele was not associated with UC in Jewish subjects to a statistically significant degree (page 29). The specification does not provide any information on the frequency of the H2 allele in female subjects or in non-Caucasian subjects. Thereby, one cannot ascertain the relationship between the H2 allele and the occurrence of thrombosis or sensitivity to thienopyridines in non-Caucasian subjects and female subjects. The unpredictability of establishing a correlation between a polymorphism or a haplotype and a disease is well accepted in the art. For example, Hirschhorn et al. (Genetics in Medicine. 2002. 4(2): 45-61) teaches that most reported associations between genetic variants and diseases are not robust. Hirschhorn states that "of the 166 putative associations studied three or more times, only 6 have been consistently replicated" (see abstract). The reference sets forth a number of reasons for the

irreproducibility of these studies, suggesting that population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn concludes that "the current irreproducibility of most studies should raise a loud cautionary alarm" (page 60, col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Regarding the fact that the claims encompass indirectly detecting the H2 haplotype and detecting one polymorphism in a $P2YP_{12}$ receptor gene haplotype by analyzing any region around positions 139, 744, and 801 of intron 1 and position 52 of exon 2, it is unpredictable as to what would be the identity of additional polymorphisms and haplotypes associated with thrombosis and response to thienopyridine therapy. The unpredictability of identifying additional polymorphisms associated with thrombosis and response to thienopyridine therapy is supported by the teachings in the specification wherein it is disclosed that while the H2 haplotype is associated with maximal ADP-induced aggregation, the C34T polymorphism is not associated with maximal ADP-induced aggregation (page 17).

Moreover, the claims encompass determining susceptibility to thrombosis or sensitivity to a thienopyridine in any mammal or other vertebrate. However, the specification does teach the occurrence of H2 haplotype in a representative number of non-human mammalian or vertebrate subjects. Without extensive information regarding the structure-function relationship between the H2 haplotype and thrombosis or

response to compounds that prevent platelet aggregation, it is highly unpredictable as to whether the H2 haplotype will occur in a representative number of non-human mammalian or vertebrate subjects and will be associated with the occurrence of PAD or other types of thrombosis, or response to thienopyridine compounds.

The unpredictability of extrapolating the results obtained from one organisms (humans) to other organisms, and from one ethnic group to other ethnic groups is emphasized by the teachings of Halushka (Nature. July 1999. 22: 239-247). Halushka studied the frequency of polymorphisms among different ethnic populations and between human and apes. The reference (see abstract, page 244 col. 2 and page 245, col 1) found that there was considerable diversity in the number and frequency of SNPs between different ethnic groups and between humans and orthologous great ape sequences.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The claims encompass methods of indirectly detecting the H2 haplotype and detecting one polymorphism in a $P2YP_{12}$ receptor gene haplotype by analyzing any region around positions 139, 744, and 801 of intron 1 and position 52 of exon 2. Thereby, the claims encompass detecting a biological activity as indicative of the presence of the H2 haplotype. However, the specification does not provide sufficient guidance for indirectly detecting the H2 haplotype or a polymorphism in the $P2YP_{12}$ receptor gene by assaying for a biological activity that is specifically indicative of the H2 haplotype.

The claims also encompass methods in which a polymorphism is detected by assaying for a polymorphism or haplotype in linkage disequilibrium with one of the polymorphisms of the H2 haplotype. However, the specification does not provide sufficient guidance as to how to predictably identify polymorphisms and haplotypes in linkage disequilibrium with the H2 haplotype and individual polymorphisms of the H2 haplotype, such that said newly identified polymorphisms and haplotypes could be used to diagnose risk of thrombosis or sensitivity to thienopyridine therapy. Extensive experimentation would be required to identify additional polymorphisms associated with PAD and to determine the association between the H2 haplotype and other forms of thrombosis or response to thienopyridine treatment in human and non-human male and female subjects. For example, such experimentation may involve sequencing the $P2YP_{12}$ receptor gene of individuals having PAD to identify novel polymorphisms in the $P2YP_{12}$ receptor gene, sequencing the $P2YP_{12}$ receptor gene of individuals that do not have PAD, determining the frequency of any polymorphisms that are present in the individuals having PAD and not present in individuals that do not have PAD, and performing a statistical analysis to determine whether there is a statistically significant increase or decrease in the occurrence of a novel polymorphism in individuals having PAD as compared to individuals that do not have PAD Further experimentation may also include performing the above method in a representative number of human subjects having and not having other thrombosis disorders, such as subjects having a risk of heart attaches or stroke. Additionally, the experimentation may include performing the above methods in a representative number of male and female subjects

from different ethnic groups, such as Europeans, Asians, African Americans etc, and in a representative number of non-human subjects, such as cats, dog, sheep, horses etc. The experimentation may also include trying to develop alternative, indirect methods which specifically allow for the detection of the H2 haplotype, such as assays that would detect an allele that is fully in linkage disequilibrium with the H2 haplotype or individual polymorphisms in the H2 haplotype or assays that detect a specific biological activity associated with the H2 haplotype. The outcome of such experimentation cannot be predicted and is thus considered to be undue.

While methods for sequencing nucleic acids are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a particular phenotype. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional polymorphisms associated with the occurrence of PAD or other types of thrombosis in human or non-human subjects.

Working Examples:

The specification provides a working example in which an association between the presence of the H2 haplotype and PAD was determined in Caucasian male subjects.

No working examples are provided wherein sensitivity to ticlopidine or clopidogrel, or other thienopyridine derivatives is diagnosed by assaying for the presence of the H2 haplotype.

No working examples are provided wherein the presence of the H2 haplotype is detected as a means for effectively diagnosing the risk of developing any disorders other than PAD, including vein thrombosis, stroke, heart attack etc.

No working examples are provided wherein the presence of other individual polymorphisms or haplotypes in linkage disequilibrium with the H2 haplotype are detected of the presence of the H2 haplotype and risk of developing thrombosis.

No working examples are provided in which thrombosis is diagnosed by indirectly assaying for the H2 haplotype using, for example, a biological activity assay or an assay.

No working examples are provided wherein non-Caucasian subjects, female subjects or non-human mammalian or vertebrate subject's are analyzed for the presence of the H2 haplotype as diagnostic of risk of developing thrombosis or sensitivity to thienopyridine therapy.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v*

Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification only an association between the H2 haplotype in Caucasian male subjects and the occurrence of peripheral arterial disease. The specification has not established a clear association between the H2 haplotype and sensitivity to ticlopidine or clopidogrel, or other thienopyridine derivatives. Further, the specification has not teach an association between the H2 haplotype and PAD or other forms of thrombosis in a representative number of non-Caucasian subjects, in female subjects of any ethnic background, or in a representative number of non-human mammalian or vertebrate subjects. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6, 7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Muzny (GenBank Accession No. AC024886; cited in the Office action of March 27, 2007).

It is noted that the present claims are considered to be limited to a method comprising the step of analyzing a genomic DNA obtained from a biological sample in a region of the $P2YP_{12}$ receptor gene located around positions 139, 744, 801 of intron 1 and position 52 of exon 2. As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation". In the present situation, the claim language of "for identifying at least one polymorphism of a haplotype of the $P2YP_{12}$ receptor associated with thrombosis in a subject or associated with lower sensitivity toward a thienopyridine therapy" is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Accordingly, the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight.

Muzny teaches a method comprising analyzing genomic DNA of a biological sample in a region of the $P2YP_{12}$ receptor gene, wherein the region comprises the complete coding and non-coding sequence of the $P2YP_{12}$ receptor gene. The $P2YP_{12}$ receptor sequence disclosed by Muzny includes each of the polymorphisms located at positions 139, 744, 801 of intron 1 and position 52 of exon 2 of the $P2YP_{12}$ receptor gene (see nucleotide sequence beginning at nucleotide position 125834). Regarding claim 7, since Muzny teaches that the BAC RP11-25K24 genomic DNA clone was sequenced, the genomic DNA was necessarily extracted from a biological sample. Regarding claim 9, Muzny teaches that the analysis is performed by sequencing (see the "Comment" section of Muzny). Thereby, Muzny anticipates the claimed invention.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny in view of Soper (U.S. Patent No. 5,846727).

The teachings of Muzny are set forth above. Muzny teaches sequencing of a genomic nucleic acid sample, but does not teach performing PCR prior to sequencing. However, it was conventional in the art at the time the invention was made to amplify sample nucleic acids by PCR prior to sequencing. For example, Soper (see abstract) teaches a rapid and cost-effecting means for sequencing DNA wherein the DNA is amplified by PCR prior to performing the sequencing steps.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Muzny so as to have amplified portions of the DNA by PCR, including the region containing the P2Y12 receptor sequences, prior to sequencing in order to have further increased the quantity of the DNA, thereby facilitating the sequencing and analysis of the DNA.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634

Notice to Comply	Application No. 10/531286	Applicant(s) Aiach et al	
	Examiner Carla Myers	Art Unit 1634	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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